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LYMPHOGRANULOMA INGUINALE IN THE MALE IN LIVERPOOL, ENGLAND, 1947 TO 1954*†

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Introduction

Probably the earliest reference to lymphogranuloma inguinale was made in 1786 by an Englishman, the great John Hunter, who described a condition in which buboes developed without apparent cause and an application of mercury had no effect. The classical biography of the condition is by another Englishman, Stannus (1933), but the disease is, nevertheless, not a common condition in Great Britain. No precise figures are available before 1949. Since that date, however, the condition has been listed separately in the returns required by the Ministry of Health from the Venereal Disease Clinics in England and Wales and during the quinquennium 1949 to 1953 cases reported have averaged about fifty per year (Table I). In contrast, no less than 2,494 cases were reported in the clinics of the United States of America in 1948.

TABLE I

LYMPHOGRANULOMA INGUINALE IN GREAT BRITAIN

Year	Males	Females
1953	71	5
1954	61	3
1955	81	8

Infection is commonly acquired abroad and the vast majority of cases occur among seafarers calling in at the great ports. Opportunities for observing the condition are particularly good in Liverpool which has a considerable trade with native peoples throughout the world, among whom lymphogranuloma is endemic. In fact, somewhere between a quarter and a third of all cases of lymphogranuloma inguinale reported in Great Britain are first seen at one particular Liverpool clinic, the Seamen's Dispensary, which, under the directorship of the late Dr. A. O. F. Ross, became world famous as a centre for the diagnosis and treatment of venereal disease (Table II).

TABLE II

LYMPHOGRANULOMA INGUINALE AT SEAMEN'S DISPENSARY, LIVERPOOL

Year	Cases
1949	22
1950	17
1951	19
1952	20
1953	15
1954	22

The following is not intended as a comprehensive review of lymphogranuloma inguinale, but deals with the condition as we encountered it amongst male patients admitted to our wards during the years 1947 to 1954.

Material

During the period under review, 55 cases of lymphogranuloma were admitted to the wards; some of the cases have already been reported separately elsewhere (Alergant, 1950 and 1953). In many instances, a period in hospital was not strictly necessary on medical grounds, but was arranged for social or other reasons. Ages ranged from 18 to 59 years (average 29·5). Twenty-five of the patients were Europeans, mainly British and Scandinavian, nine were Chinese, nine were Indian, eight were African Negroes, three were Burmese, and one South American. In all cases the infection appears to have been acquired abroad, but with some patients linguistic difficulties prevented us from ascertaining the exact locality. Only four patients had acquired their infection in European countries: two in Portugal, one in Spain, and one in Italy. Of the infections acquired outside Europe, the largest number imported from any single country was eight from Brazil, but the eastern hemisphere contributed far more to the total than did the western. Despite the extensive sea-borne traffic between Liverpool and the eastern seaboard of the United States of America and the endemic nature of lymphogranuloma inguinale there, it is surprising to note that in no case did infection appear to have been acquired in that country. The shorter trip across the Atlantic compared with the average trip to and from the Far East may be the explanation, but a shortage of dollars amongst British seamen may be another factor.

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Results of Clinical Investigation

The incubation period was recorded in 45 instances. Many of the patients, however, had repeatedly exposed themselves to infection in the months preceding the onset of symptoms, so that estimates of the incubation period are likely to be only approximate; the extremes recorded were one week and 14 weeks. In only eight cases was the incubation period recorded as being over 6 weeks, and in only four, as under 2 weeks. Thus, in 33 of the 45 cases recorded, it varied between 2 and 6 weeks (Figure). In all instances the incubation period refers to the length of time between the presumed infective exposure and the development of inguinal swellings.

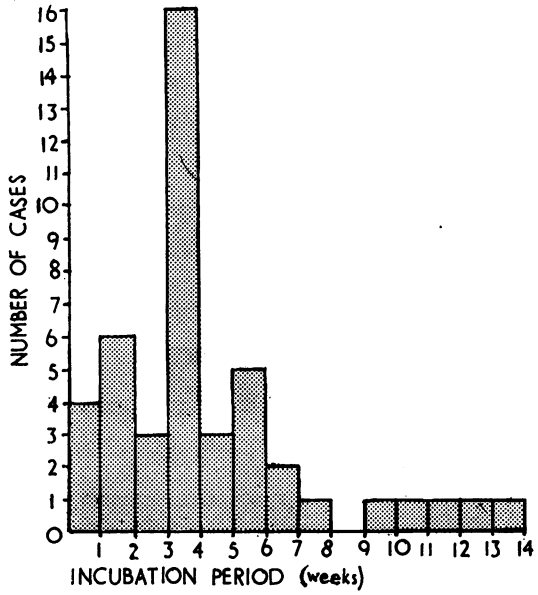

FIGURE.—Histogram illustrating variations of length of incubation in lymphogranuloma inguinale.

A history of a primary sore preceding the glandular swelling was obtained in thirteen cases (23·6 per cent.). This may be compared with the 33·3 per cent. reported by Costello and D'Avanzo (1948) and a little over 50 per cent. reported by Sézary and Drain (1954). In only two cases was a sore still present at the time of admission. One of these patients had a typical herpetiform lesion near the coronal sulcus, but the second one had an indurated preputial sore, which was at first thought to be a syphilitic chancre. Recent small herpetiform scars, however, were observed in a number of cases.

With one exception, all the patients presented with inguinal and/or femoral buboes, the latter being bilateral in thirteen patients and unilateral in the remainder. Where it was unilateral it was left-sided in 24 cases and right-sided in sixteen, while in two instances the side was not recorded. Palpable enlargement of iliac glands was noted in fifteen patients; when present this was invariably on the same side as the inguinal adenopathy. Although extension to adjacent femoral glands was frequently noted, a well-marked "sign of the groove" was seen in only two instances.

Constitutional symptoms were mostly absent. The majority of patients were apyrexial on admission to hospital and remained so throughout their stay. A temperature of 100°F. or over was recorded in twelve patients; pyrexia appeared to be associated with pus formation rather than with the extent of the glandular enlargement, and it is noteworthy that aspiration was required almost exclusively in this group.

Complications were rare. Transient joint effusions were noted in two patients, in one of whom they were associated with an erythema nodosum. A third patient developed a thrombosis of the superficial veins of the thigh, and because of persistent pain, aggravated by movement, in the region of the hip, it was thought that extension to the capsule of the hip joint may have occurred.

Eleven patients had other venereal conditions in addition to lymphogranuloma; the most common was latent syphilis, which was diagnosed in six instances. Two patients, however, presented with sero-positive primary syphilis co-incidentally with lymphogranuloma inguinale, whilst a third had a florid secondary syphilide. The remaining two patients had an acute gonococcal urethritis, the only ones in this series in whom a urethral discharge was observed.

False Positive Serological Tests for Syphilis

All patients had a Wassermann reaction performed on admission to hospital. When this was reported as negative, it was, in general, not repeated. With doubtful or positive results, however, and in the absence of any clinical evidence of syphilis, repeated Wassermann and Meinicke tests were performed in an endeavour to distinguish between associated latent syphilis and biologic false positive reactions. This problem arose in fourteen cases, excluding the three patients with early syphilis. Unfortunately, the treponemal immobilization test was not readily available in Great Britain before 1954, and as a last resort the decision had to be made on the clinical and serological evidence available. As a result, six patients were considered

to be suffering from latent syphilis, while in eight patients the results were considered to be biologic false positives. The percentage of biologic false positives (16·6 per cent.) found in this series corresponds fairly closely to the 20 per cent. found by Moore and Mohr (1952b). This conclusion is contrary to the views of Simpson (1954), who found that the incidence has been much overestimated and is probably no greater than might be found by frequent serum-testing in many of the acute bacterial and viral infections. The presence of early syphilis in three cases did not appear to affect either the Frei or lymphogranuloma inguinale complement-fixation tests.

Diagnosis

Although we do not regard the diagnosis of lymphogranuloma as entirely a laboratory procedure, pathological investigations were carried out in every case. Only two tests were used as a routine procedure, namely the Frei intradermal test and the complement-fixation test. The Frei antigen used was "Lygranum" (Squibb). Human antigen prepared after the manner originally described by Frei was used for parallel testing in a few selected cases. The antigen used in the complement-fixation test was invariably a chick embryo yolk sac preparation and the tests were performed either in Professor Downie's laboratory in Liverpool, or in Professor Bedson's laboratory in London.

Of the two tests the complement-fixation test was found to be the more useful; in 53 out of 54 cases tested, titres of 1/20 or over were found. The highest titre recorded was 1/320, but it is possible that higher titres might have been found if the reaction had been performed at higher dilutions. In fact, tests were seldom put up at a dilution higher than 1/80 in order to economize in antigen, which was difficult to obtain during most of this period.

The Frei test on the other hand was found to be positive in only 35 cases, whereas it was negative in eleven and recorded as doubtful in five. In four cases the test had to be omitted because of temporary difficulty in obtaining antigen. In eight cases initially negative or doubtful, Frei tests were repeated at intervals varying from a few days to 6 weeks, but only one additional positive was obtained. The high percentage of negative Frei reactions is perhaps a little surprising. Although the series consisted entirely of early cases of lymphogranuloma with symptoms which had lasted on an average only a week or two before admission, it is generally held that the Frei test becomes positive before the complement-fixation test. Our experience clearly does not bear this out, but is in accord with the views expressed by Ross (1951), who stated: "Of the two tests, probably the complement-fixation test is the more sensitive and has the merit of giving positive results earlier in the course of the disease".

There appeared, moreover, to be no correlation between the titre of the complement-fixation test and the Frei test. Negative Frei tests were found with complement-fixation titres as high as 1/320, whereas titres as low as 1/20 were associated with undoubtedly positive Frei tests.

According to Canizares (1954), repeated injections of Frei antigen do not sensitize the patient. We found, however, that, where repeated testing with chick embryo antigen was carried out, giant reactions tended to occur in some patients in the control arm (Alergant, 1950). This difficulty could be overcome by using human antigen.

No other diagnostic tests were used as a routine. A few attempts to culture the virus from bubo pus on chick embryo yolk sac were made at our request in Professor Downie's laboratories, but were unsuccessful. Demonstration of the virus in stained smears, using Macchiavello's stain, was successful in one or two cases and was used for demonstration purposes.

Biopsy was not used at all in the present series, but it is worth recording, in passing, that two patients were admitted to our wards with a clinical diagnosis of lymphogranuloma inguinale, in whom biopsy was necessary to establish a diagnosis. One proved to be a case of Hodgkin's disease (lymphadenoma), and the other of lymphatic leukaemia.

The cerebrospinal fluid was examined in a number of cases and was invariably found normal as far as cell count, protein, globulin, and Lange colloidal curve were concerned. No biologic false positive Wassermann reactions were encountered.

Although several observers have demonstrated the virus of lymphogranuloma in the cerebrospinal fluid, less interest has been shown in the presence of antibody. In an attempt to determine whether antibody could be detected in the cerebrospinal fluid of patients whose spinal fluid was otherwise normal, complement-flxation tests were performed on the fluid of five patients. In all cases the test was reported as negative. This investigation is still proceeding.

The antigenic properties of cerebrospinal fluid have been discussed by a number of observers (Midana and Vercellino, 1934; Ottolina, 1941). Undiluted cerebro-spinal fluid sterilized according to the original Frei recipe was given intradermally in a dose of 0·1 ml. to three patients with positive Frei tests but it failed to produce a skin reaction in any of the cases.

Treatment

Before 1949, penicillin and the sulphonamides were the only drugs available for the treatment of lymphogranuloma inguinale. Previous experience had convinced us that penicillin was of doubtful value, and consequently, during this period, patients were treated with sulphonamides. Sulphathiazole was the preparation used almost exclusively. The dosage favoured was 1 g. four times a day for 10 to 14 days, repeating the course if necessary after an interval of 1 to 2 weeks.

Following the work of Wright, Sanders, Logan, Prigot, and Hill (1948), we treated a series of cases with aureomycin. Our earlier results have been published elsewhere (Alergant, 1950). Initially we used a dosage of 250 mg. 6-hourly for 7 days. Subsequently the dose was doubled and the period of treatment was prolonged to from 10 to 14 days. In general, we are not convinced that the results obtained with this relatively expensive antibiotic are any better than those which can be obtained with the much cheaper sulphonamides. Terramycin does not appear to offer any advantages over aureomycin, while chloramphenicol is, if anything, less effective, but our experience with these last two drugs is limited.

It is our present practice in 1956 to treat all cases initially with sulphonamides and to reserve aureomycin for cases which respond poorly or incompletely. We have previously observed (Alergant, 1953) that some patients appear to derive more benefit when two different drugs are exhibited successively, than from any single drug. The demonstration by Hurst, Landquist, Melvin, Peters, Senior, Silk, and Stacey (1953) of the effectiveness of quinoxaline, 1 : 4, dioxide and certain of its substituted derivatives against lymphogranuloma inguinale in mice, and of its effectiveness in developing chick embryos, led to a request for a trial of one of the most active of these compounds in human lymphogranuloma. The compound selected was 2 : 3 dimethyl quinoxaline, 1 : 4 dioxide (7218). In all, seventeen patients were treated with this compound. Our experience with it has been detailed elsewhere (Alergant, 1953). Suffice it to say that toxic side-effects prevent this therapeutically active compound from being a useful addition to the pharmacopoea.

Aspiration of buboes was found necessary in nine cases and in some of these on more than one occasion. Otherwise local treatment was not considered important. Hot fomentations, much favoured by our nursing staff, was thought to encourage softening and to increase the necessity for aspiration.

Prognosis

The prognosis in early lymphogranuloma inguinale in the male is, in our experience, uniformly good. Pain and tenderness are rapidly controlled, periadenitis resolves, and there remains a residuum of discrete mobile painless glands, normal, or a little larger than normal, in size. In some cases, however, thickening along the line of the inguinal ligament may persist for a considerable time. Sinuses, when they form, normally do not persist for more than a few weeks, and in only one case was surgical excision of a sinus necessary in order to obtain healing. Complications were found to be rare and of a benign and transient nature. No relapses were observed. The effect of therapy on the Frei and complement-fixation test was difficult to evaluate, as it was impossible in the majority of cases to keep the patient under observation for a sufficient length of time.

In a small series of cases treated with aureomycin and kept under observation for from 6 to 14 weeks following treatment, it was found that no patient initially Frei-positive became Frei-negative, but two patients initially positive gave doubtful reactions, one 3 months and the other a month after completion of treatment. The complement-fixation test generally remained at its initial level after treatment, but in one case a pre-treatment titre of 1/80 had become negative at the end of 3 months. In another case, however, a titre of 1/20 before treatment had risen to 1/320 2 months after a successful course of treatment.

Summary

Although it is not a common condition in Great Britain, better opportunities for the observation of lymphogranuloma inguinale are afforded by Liverpool than by any other town or city in the United Kingdom. Our experience with 55 cases of early lymphogranuloma in the male, observed in hospital during the years 1947 to 1954, is recorded, and the superiority of the complement-fixation test over the Frei test in the diagnosis of early cases is stressed. We regard it as essentially a benign condition, and give sulphathiazole or some other suitable sulphonamide as the drug of choice, reserving aureomycin for cases which respond incompletely or unfavourably.

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DISCUSSION

(1) **Dr. Macfarlane** (*Newcastle-on-Tyne*), complimenting Dr. Alergant on his excellent paper, asked if he had had any experience in the treatment of the tertiary phase of the disease in women. In one particular instance, he had found recurrent ulceration and granulation-tissue formation in the genital region. Extensive and varied antibiotic schedules of chemotherapy had failed to produce permanent satisfactory results. Dr. Alergant, in reply, said that unfortunately he had had little experience in the treatment of this phase of lymphogranuloma infection.

(2) **Dr. Neville Mascall** (*London*) stated that he had been treating a chronic case of lymphogranuloma venereum, the main symptom of which was a discharging anal fistula. Prolonged courses of achromycin and terramycin had been given, also sulphadiazine and thalistatyl. The best progress seemed to be made when the patient was taking the sulpha drugs, especially thalistatyl. The sinus healed but unfortunately kept breaking down again. The blood titre at the beginning of treatment was 1/128, and so far, despite extensive treatment, no change had occurred. Frei's test was positive.

(3) **Dr. McElligott** (*London*) agreed that the complement-fixation test was on the whole a more useful diagnostic aid than the skin test using "Lygranum", which often gave anomalous results. He found that most uncomplicated cases responded well to sulphonamides, and that the proctitis, which so often accompanied the pelvi-rectal syndrome, was helped by retention enemata of 20 per cent. sulphaguanidine, after a preliminary bowel wash with a dilute solution of permanganate of potash, as described by Rajam and Rangiah (1955).

(4) **Dr. A. J. Gill** (*Manchester*) raised the question of the difficulty in cases of lymphogranuloma inguinale (LGV) in deciding whether they were fresh infections or not. It was common experience that a positive Frei test was a long lasting if not permanent sensitivity. Also, as the period of treatment for LGV was so short, it did not interfere materially with antibody formation and the titre in the complement-fixation test went on rising or remained very high for at least 2 years after infection. Positivity in these tests was good evidence of an LGV infection acquired perhaps years previously but, particularly where history-taking was difficult, there remained the doubt that the case might be an old one with perhaps a superadded septic adenitis.

(5) **Dr. Elisabeth Rees** (*Liverpool*) had seen two cases of lymphogranuloma in females at the Royal Infirmary, Liverpool, in the past 5 years. The first was an acute case with inguinal and femoral adenopathy demonstrating the "sign of the groove". The Frei test was negative and the complement-fixation test positive. The patient responded to treatment with sulphonamides. The second was a late case but presented no treatment difficulties because, when first seen, her rectum had already been removed by the surgeons who had diagnosed her complaint as carcinoma of the rectum. The true diagnosis was made by the pathologist on histological examination of the specimen. The Frei test was negative and the complement-fixation test positive. This patient was treated with terramycin.

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